[CONTRIBUTION FROM STERLING-WINTHROP RESEARCH INSTITUTE]

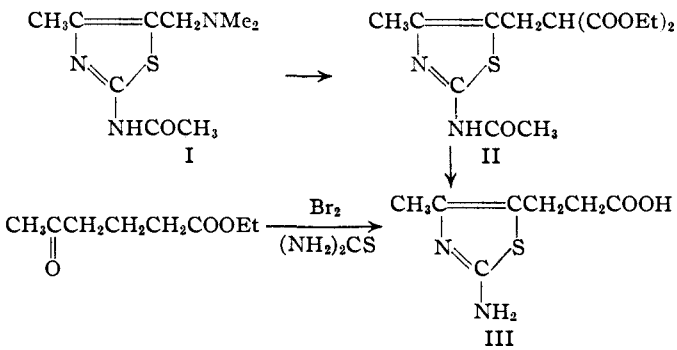
Alkylation with Non-ketonic Mannich Bases. Aminothiazoles and Pyrrole

BY NOEL F. ALBERTSON

Several years ago it was observed independently, both in this Laboratory and elsewhere, that gramine, 3-(dimethylaminomethyl)-indole, or one of its quaternary salts could be employed to alkylate malonic ester,[1,2] and this fact was used to develop a synthesis of tryptophan.[2,3] At that time the dialkylaminomethylindoles were the only reported examples of non-ketonic Mannich bases which can serve as alkylating agents for reactive methylene compounds. In fact, gramine was unique not only in its reaction but also in its preparation as compared with all of the other examples of Mannich bases compiled by Blicke.[4] The synthesis of gramine involves the introduction of a dialkylaminomethyl group directly onto a carbon atom in a ring which does not contain a ketonic or phenolic group.

It appeared unlikely that gramine should be so unique. On the contrary, it seemed probable that heterocyclic compounds of a phenolic nature, which contain a suitably activated hydrogen atom, would undergo the Mannich reaction to form "allylic" amines which could, in turn, serve as alkylating agents.

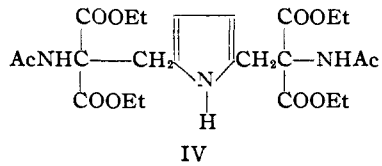
To test this supposition 2-acetamido-4-methylthiazole was treated with dimethylamine and formalin in acetic acid. From the reaction mixture a compound was obtained which, based on analysis, was the Mannich amine I. Sodioacetamidomalonic ester was readily alkylated by this base, in the form of its methyl sulfate, to give diethyl 5-(2-acetamido-4-methylthiazylmethyl)-acetamidomalonate. Since it has been pointed out by Bodendorf and Koralewski[5] that amides react with formalin and amines, an alternative structure for the Mannich base must be considered wherein the dimethylaminomethyl group is on the amide nitrogen. The fact that acetamide failed to react under the conditions under which 2-acetamido-4-methylthiazole reacted militated against this structure. Direct proof that the substitution actually took place on the ring rather than on the amide nitrogen was obtained by using the Mannich base (I) to alkylate malonic ester. The product obtained (II) was hydrolyzed and partially decarboxylated to yield III, a propionic acid which proved to be identical with that synthesized by interaction of ethyl γ-acetobutyrate, bromine and thiourea, and subsequent hydrolysis. The establishment of structure III for the propionic acid is indirect proof of the structure of the Mannich base (I).



When 2-acetamidothiazole was substituted for 2-acetamido-4-methylthiazole it also gave a Mannich base which served as an alkylating agent.

As one would expect, elimination of the 2-acetamido group greatly diminished the reactivity of the thiazole nucleus toward this type of reaction. 2,4-Dimethylthiazole gave a very minute yield of an unidentified product in the Mannich reaction. 2-Methyl-4-phenyloxazole gave only the acetate when treated with dimethylamine and formalin in acetic acid. A single attempt to use 2-(dimethylaminomethyl)-thiophene as an alkylating agent was unsuccessful.

The alkylation of acetamidomalonic ester with 2-(dimethylaminomethyl)-pyrrole has been reported recently.[6] Before the appearance of this work we had found that it is possible to replace not only the amino group of a monosubstituted pyrrole, but that both amino groups of a 2,5-bis-(aminomethyl)-pyrrole may be eliminated in an alkylation reaction. Thus, 2,5-bis-(piperidinomethyl)-pyrrole[7] reacted with acetamidomalonic ester to give ethyl pyrrole-2,5-bis-(2-acetamido-2-carbethoxypropionate), IV.



IV

(1) Snyder, Smith and Stewart, THIS JOURNAL, **66**, 200 (1944).

(2) Albertson, Archer and Suter, *ibid.*, **66**, 500 (1944).

(3) (a) Snyder and Smith, *ibid.*, **66**, 350 (1944); (b) Albertson, Archer and Suter, *ibid.*, **67**, 36 (1945); (c) Howe, Zambito, Snyder and Tishler, *ibid.*, **67**, 38 (1945); (d) Albertson and Tullar, *ibid.*, **67**, 502 (1945).

(4) Blicke, "The Mannich Reaction" in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942.

(5) Bodendorf and Koralewski, *Arch. Pharm.*, **271**, 101 (1933).

(6) Herz, Dittmer and Cristol, "Preparation of Some Monosubstituted Derivatives of Pyrrole by the Mannich Reaction," presented before the 111th meeting of the A. C. S. at Atlantic City N. J. THIS JOURNAL, **70**,504 (1948).

(7) Bachman and Heisey, THIS JOURNAL, **68**, 2948 (1946).

Experimental

2-Acetamido-4-methyl-5-(dimethylaminomethyl)-thiazole (I).[8]—A mixture of 15.6 g. of 2-acetamido-4-methylthiazole, 8 ml. of 37% formalin solution and 25 ml. of a solution of dimethylamine in glacial acetic acid (equivalent to 0.11 mole of amine) was warmed for seven hours on a steam-bath. Then 50 ml. of water was added, the solution made basic with potassium carbonate and extracted with five 50 ml. portions of chloroform. Removal of the solvent *in vacuo* left 25.9 g. of viscous residue. This was dissolved in alcohol and acidified with alcoholic hydrogen chloride. The crude hydrochloride was filtered and washed with alcohol; yield 23.0 g. (92%), m. p. 208–210°. This material was used for alkylation. A sample, recrystallized from aqueous acetone, melted at 223°.

Anal. Calcd. for $C_9H_{15}N_3OS \cdot HCl$: S, 12.84. Found: S, 12.64.

The free base, m. p. 138–139.5°, may be obtained by treating the hydrochloride with aqueous sodium carbonate. However, the hydrochloride is just as satisfactory for alkylation reactions as is the free base provided sufficient sodium ethylate is employed.

2-Acetamido-5-(dimethylaminomethyl)-thiazole.—This compound was prepared in the same manner as the analogous 4-methylthiazole; m. p. 248–249°.

Anal. Calcd. for $C_7H_{11}N_3OS \cdot HCl$: Cl, 15.04; S, 13.60. Found: Cl, 15.10; S, 13.51.

2-Acetamido-5-(piperidinomethyl)-thiazole.—This compound was prepared in the manner described above; m. p. 159–161.5° (free base).

Anal. Calcd. for $C_{11}H_{17}N_3OS$: C, 55.21; H, 7.16; N, 17.56. Found: C, 55.43; H, 7.13; N$_k$, 17.25.

Diethyl 5-(2-acetamido-4-methyl) thiazylmethylacetamidomalonate.—To a solution of 0.93 g. of sodium in 75 ml. of absolute alcohol was added 8.80 g. of acetamidomalonic ester, 7.2 g. of crude 2-acetamido-5-(dimethylaminomethyl)-4-methylthiazole (free base) and 6.3 ml. of dimethyl sulfate. It was necessary to cool the reaction flask in ice water occasionally. After four hours the reaction mixture was poured onto 200 g. of water–ice mixture containing 2.4 ml. of acetic acid. The white crystals (6.5 g.) were filtered, washed and dried; m. p. 183°. A sample for analysis, recrystallized from aqueous alcohol, melted at 183.5°.

Anal. Calcd. for $C_{16}H_{23}O_6N_3S$: C, 49.86; H, 6.01; N, 10.90. Found: C, 49.70; H, 6.09; N, 10.56.

Diethyl 5-(2-Acetamidothiazylmethyl)-acetamidomalonate.—This product was prepared in the same manner as the analogous 4-methylthiazole except that the hydrochloride rather than the free Mannich base was used. An additional amount of sodium ethylate (equivalent to the hydrochloride) was used in the reaction; m. p. 224–225°.

Anal. Calcd. for $C_{15}H_{21}N_3O_6S$: N, 11.31; S, 8.63. Found: N, 11.30; S, 8.80.

Diethyl 5-(2-Acetamidothiazylmethyl)-malonate.—This was prepared in the same manner as the above two compounds by substituting malonic ester for acetamidomalonic ester, m. p. 150.5–152°.

Anal. Calcd. for $C_{13}H_{18}N_2O_6S$: S, 10.20. Found: S, 10.29.

β-[5-(2-Amino-4-methylthiazyl)]-propionic Acid (A) from Mannich Base.—To 1.45 g. of sodium in 100 ml. of dry alcohol was added 15 ml. of malonic ester, 6.6 g. of 2-acetamido-5-dimethylaminomethyl-4-methylthiazole hydrochloride and 4.9 ml. of dimethyl sulfate. The reaction mixture was cooled by swirling in ice water. After four hours the reaction mixture was poured onto ice and water containing 3 ml. of acetic acid. The product was extracted with chloroform. The solvent and excess malonic ester were removed on a steam-bath under 2 mm. pressure and the residual 4.2 g. of oil hydrolyzed by refluxing for two hours with 20 ml. of hydrochloric acid (1:1). The solution was charcoaled, filtered and concentrated *in vacuo*. The viscous yellow residue was dissolved in 10 ml. of water and the *p*H brought to 7 with ammonium hydroxide. The solution slowly deposited crystals of the acid, m. p. 253–257° dec.

Anal. Calcd. for $C_7H_{10}N_2O_2S$: S, 17.22; N, 7.52. Found: S, 17.52; N, 7.30.

(B) **From Ethyl γ-Acetobutyrate.**—Ethyl γ-acetobutyrate was prepared as described below. To a suspension of 15.8 g. of ethyl γ-acetobutyrate and 15.2 g. of thiourea was added 15.9 g. of bromine with shaking.[9] After all of the bromine had been added the mixture was warmed for two and one-half hours on the steam-bath whereupon it became brown. A small amount of water was added, the mixture warmed and the clear solution treated with charcoal. Addition of ammonium hydroxide to a sample of the filtrate gave a black unpromising solution from which an oil slowly separated. Consequently, the main filtrate was warmed for forty minutes on the steam-bath to effect hydrolysis. The solution was filtered from sulfur and neutralized with ammonium hydroxide. The acid which precipitated was filtered, washed with water, alcohol and ether; yield 9.1 g. The product can be purified by reprecipitation from sodium hydroxide solution with acetic acid or from hydrochloric acid solution with ammonium hydroxide. The product melted at 254–256° and when mixed with the acid prepared by method A also melted at 254–256°.

γ-Acetobutyric Acid.—Condensation of methyl acrylate with a two-fold excess of acetoacetic ester in the presence of sodium ethylate gave a 73% yield of β-(carbomethoxyethyl)-acetoacetic ester as a pale yellow oil, b. p. 109–110° at 2 mm., $n^{25}D$ 1.4385.

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.24; H, 7.46.

Hydrolysis of β-(carbomethoxyethyl)-acetoacetic ester was effected by refluxing with concentrated hydrochloric acid (3 ml. per g.) until evolution of carbon dioxide ceased. Most of the water was then removed *in vacuo* until the monohydrate started to crystallize. Water of crystallization was removed by addition of benzene and azeotropic distillation. The γ-acetobutyric acid boiled at 107.5–109° (5 mm.); yield, 85%.[10]

Esterification[11] yielded the ethyl ester (67%), b. p. 52–59° (1 mm.), which was used without further purification.

Ethyl 2,5-Pyrrole-bis-(2-acetamido-2-carbethoxypropionate).—Sodium (3.3 g.) was dissolved in 200 ml. of dry ethanol. There was then added 31 g. of acetamidomalonic ester,[12] 7.8 g. of 2,5-bis-(N-piperidinomethyl)-pyrrole[7] and 11.0 ml. of dimethyl sulfate. After twelve hours the mixture was diluted with water and extracted with chloroform. Evaporation of the chloroform gave a crystalline residue in practically quantitative yield. Several recrystallizations from aqueous alcohol gave a product melting at 160–160.8° (cor.).

Anal. Calcd. for $C_{24}H_{33}N_3O_{10}$: C, 54.85; H, 6.71; N, 7.99. Found: C, 54.75; H, 6.60; N, 7.90.

Summary

2-Acetamidothiazoles, unsubstituted at position five, were found to react with formalin and dimethylamine to introduce a dimethylaminomethyl group directly onto the ring. These Mannich bases were used to alkylate malonic esters.

2,5-bis-(Piperidinomethyl)-pyrrole reacted with two moles of acetamidomalonic ester to give the symmetrically substituted pyrroledipropionate.

RENSSELAER, N. Y. RECEIVED JULY 23, 1947

(8) Bock, Johnson and Armstrong in U. S. Patent 2,409,829 (which issued after the completion of this work) describe the preparation of some Mannich bases of 2-acylaminothiazoles. No mention was made of any attempt to use these Mannich bases as alkylating agents.

(9) *Cf.* Dodson, THIS JOURNAL, **67**, 2242 (1945).

(10) Bentley and Perkin, *J. Chem. Soc.*, **69**, 1511 (1900).

(11) Vorländer, *Ann.*, **294**, 270 (1897).

(12) See ref. 3; this chemical is now commercially available.